REMARKS

Status of Claims

Claims 1-21, 23-27, and 29-80 are currently pending. Claims 7-14, 24, 29, 32-34, 50, 54-62 and 68-76 are withdrawn. Applicants submit that no amendments have been made and that no new matter has been added.

Reply to Claim Rejections under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1-6, 15-21, 23, 25-27, 30-31, 35-49, 51-53, and 63-67 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pickar *et al.* U.S. Patent No. 5,492,907 ("Pickar") in view of Beasley, Jr. *et al.* U.S. Patent No. 5,605,897 ("Beasley") or Moore *et al.* The Behavioral Pharmacology of Olanzapine, a Novel "Atypical" Antipsychotic Agent, Volume 262, Issue 2, pp. 545-551 (1992) ("Moore"). The Examiner asserted that arguments previously put forth by Applicants were unpersuasive. The Examiner argued, on page 13 of the Office Action, that while Pickar does not teach the combination of an α_2-adrenergic receptor antagonist and an atypical antipsychotic drug, Beasley teaches that olanzapine as an antagonist of dopamine at D_1 and D_2 receptors. The Examiner reasons that because Pickar teaches the combination of α_2-adrenergic receptor antagonist and a D_2 dopamine receptor antagonist and that Beasley teaches that olanzapine is a D_2 dopamine receptor antagonist that the combination of an α_2-adrenergic receptor antagonist with an atypical antipsychotic neuroleptic like olanzapine would have been obvious to one of ordinary skill in the art. Further, the Examiner argued that Moore teaches that olanzapine only causes catalepsy at higher doses, and thus would be unlikely to produce undesirable extrapyramidal symptoms. The Examiner also argued that the use of idazoxan in combination with olanzapine would be *prima facie* obvious because it is well known in the art that idazoxan and olanzapine demonstrated independent efficacy against the same disease, schizophrenia. Applicants respectfully traverse.

Applicants submit that the Examiner is not addressing the fact that the prior art teaches that atypical antipsychotics have a greater 5-HT-2 receptor antagonistic effect

than a D_2 dopamine receptor antagonistic effect and the clinical repercussions of this difference shown in the prior art. Thus, Applicants submit that the Examiner's reasoning against Applicants' previously submitted arguments for no reasonable expectation of success amount of impermissible use of official notice. Moreover, the Examiner's allegation that the improved activity shown for olanzapine would be expected also contradicts the teachings of the prior art regarding the primacy of the 5-HT-2 receptor antagonistic effect of atypical antipsychotics. Moreover, the Examiner's argument for a *prima facie* case of obviousness that idazoxan and olanzapine are shown to independently treat schizophrenia is incorrect. The prior art does not teach that idazoxan can be used to independently treat schizophrenia.

No Reasonable Expectation of Success

The Examiner's arguments refuting the Applicants' evidence regarding no reasonable expectation of success amounts to impermissible use of official notice. The Examiner has maintained the argument that it would be obvious to one of ordinary skill in the art to substitute a typical antipsychotic used in combination with an α_2-adrenergic receptor antagonist with an atypical antipsychotic despite the declaratory evidence and argument filed in the previous response. The Examiner has not addressed the arguments made by Applicants including the effectiveness of atypical antipsychotics through antagonism of the 5-HT-2 receptor, and ignored the teachings of the prior art regarding the primacy of antagonism of the 5-HT-2 receptor over the antagonism of the D_2 dopamine receptor.

Applicants assert that the Examiner is taking official notice that the antagonism of the 5-HT-2 receptor of atypical antipsychotics would not cause a difference in the expected outcome of its combination with idazoxan, despite Applicants supplying evidence to the contrary.[1] Applicants assert that the functional equivalence of typical and atypical antipsychotics, especially based on their mechanistic differences detailed in the previous Office action response, is not common knowledge or well known in the art. Applicants request that the Examiner provide specific evidence showing the equivalence of typical and atypical antipsychotics in order to demonstrate that one of ordinary skill in

[1] *See* MPEP § 2144.03.

the art would have a reasonable expectation of success when substituting an atypical antipsychotic with a typical antipsychotic in combination with an α_2-adrenergic receptor antagonist for treatment of a serious psychotic mental illness.

Unexpected Properties

The Examiner's arguments do not demonstrate that the evidence indicated by the Applicants was not unexpected. The Examiner argued that because Moore teaches that catalepsy is not observed at much higher doses of olanzapine and that olanzapine increases response during the conflict component of the modified Geller Seifter test, demonstrating that the compound has anxiolytic activity. Moreoever, the Examiner argued that idazoxan and olanzapine are effective in treating schizophrenia separately. Because of this the combination of idazoxan and olanzapine should show additive, if not, synergistic effects, rendering the data supplied with the previous response expected. Applicants respectfully traverse.

The previously submitted data shows that adjunctive treatment with a selective α_2 adrenergic receptor antagonist (idazoxan) to relatively low doses of an atypical antipsychotic with low affinity for α_2 adrenergic receptors (olanzapine) produced a significant antipsychotic-like effect without catalepsy. The present results, obtained by a combination of idazoxan and olanzapine, demonstrate an equally or more effective suppression of the CAR by the use of only 2.5 mg/kg of olanzapine. Thus, these data indicate that the dose of olanzapine required to obtain an effective antipsychotic effect may be reduced by almost 50% through the adjunct treatment with idazoxan. These results are truly unexpected.

Whether olanzapine causes side effects at this dose or a higher dose, the result is still unexpected. It would be desirable to use a lower dose of any drug for a variety of reasons. For example, some patients could be unusually sensitive, and it would be less expensive to take less drug. Thus, the Examiner's indication of the dosage at which side effects commonly occur as reported by Moore is inapposite to whether these results are unexpected.

The Examiner's arguments regarding the independent effects of idazoxan and olanzapine are incorrect. The prior art does not teach that idazoxan is independently effective for the treatment of schizophrenia. The prior art only teaches that idazoxan enhances the therapeutic effect of typical antipsychotics.[2]

The Examiner also argued that synergistic effects would have been expected for the combination of idazoxan and olanzapine based on the teachings of the prior art. Applicants respectfully disagree. Pickar teaches that the effectiveness of the combination of an α_2 adrenergic receptor antagonist and a D_2 receptor antagonist in the treatment of serious psychotic mental illness.[3] However, Beasley and Moore stress the importance of the antagonism of the 5-HT-2 receptor by olanzapine. Beasley teaches that olanzapine "shows its greatest activity at the 5-HT-2 receptor."[4] Moore teaches that "*in vivo*, olanzapine is about 8 times more potent as a 5-HT_2 antagonist than as a dopamine antagonist."[5] Thus, if based on the Examiner's reasoning, one of ordinary skill in the art would have expected similar results because of D_2 receptor antagonism, then one of ordinary skill in the art would have expected the combination of an α_2 adrenergic receptor antagonist and an atypical antipsychotic to be less effective, not more effective.

Moreoever, Moore teaches that the only other drug that had a similar side effect profile with olanzapine was clozapine.[6] Pickar teaches that the side effects associated with clozapine make use of this drug undesirable. Thus, the results are also unexpected based on the combination of teachings of Pickar and Moore. Thus, increased effectiveness of the combination of an α_2 adrenergic receptor antagonist and an atypical antispsychotic would not have been expected.

No Prima Facie Case of Obviousness

The Examiner argued that, "the use of idazoxan in combination with olanzapine would have been *prima facie* obvious to one of ordinary skill in the art because it was

---

[2] *See* Pickar at column 2, lines 35-38.
[3] *See* Pickar at the Abstract.
[4] *See* Beasley at column 12, lines 37-42.
[5] *See* Moore at page 550, left column, first full paragraph.
[6] *Id.* at pages 549-550, bridging paragraph.

well known ion the art that both idazoxan and olanzapine demonstrated efficacy against the same disease, schizophrenia."[7] As explained above, the prior art does not teach that idazoxan is independently effective in the treatment of schizophrenia. The prior art only teaches that idazoxan is effective when combined with a typical antipsychotic.

The Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).[8] The Examiner has not explained why it would be obvious to one of ordinary skill in the art to replace a typical antipsychotic with an atypical antipsychotic in combination with an α_2 adrenergic receptor antagonist despite the functional differences between the two types of antipsychotics. The Examiner has merely stated that one of ordinary skill in the art would expect any D_2 dopamine receptor antagonist to act in the same way in this context without any reasoning regarding the differing 5-HT-2 receptor antagonism so heavily stressed in the very art that the Examiner cites. Applicants assert, that, without more, the Examiner's arguments amount to conclusory statements that are not sufficient to establish a *prima facie* case of obviousness.

For all of the above reasons, Applicants submit that claims 1-6, 15-21, 23, 25-27, 30-31, 35-49, 51-53, and 63-67 are not obvious over the teachings of Pickar, Beasley and/or Moore and respectfully request that this rejection be withdrawn.

Reply to Double Patenting Rejection over U.S. Patent No. 5,492,907

Claims 1, 2, 3, 5, and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of Pickar in view of Beasley or Moore. Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is **not patentably distinct** from the

[7] *See* the Office action at the bottom of page 13.
[8] *Also see* MPEP § 2142.

subject matter claimed in a commonly owned patent. See MPEP § 804(II)(B)(1)(emphasis in original). Further, a double patenting rejection of the obviousness-type, is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. MPEP § 804(II)(B)(1), citing *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967).

This rejection sets forth the same rationale for combining these references as was set forth in the 35 U.S.C. § 103(a) rejection. As presented above, however, Applicants respectfully submit that the unexpected properties of the claimed invention render the subject matter of claims 1-3 and 5 of Pickar in light of the teachings of Beasley or Moore, non-obvious. Further, the claims of the present application are patentably distinct from the claims of Pickar. Accordingly, Applicants respectfully request withdrawal of this rejection.

Reply to Double Patenting Rejection over U.S. Patent No. 5,663,167

Claims 1, 2, 3, 5, and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6 and 7 of Pickar *et al.* (U.S. Patent No. 5,663,167) in view of Beasley or Moore. U.S. Patent No. 5,663,167 is related to U.S. Patent No. 5,492,907 (Pickar) cited in the above double patenting rejection. As with U.S. Patent No. 5,492,907, U.S. Patent No. 5,663,167 discloses the combination a typical antipsychotic drug with an α_2-adrenergic receptor antagonist. In combining U.S. Patent No. 5,663,167 with Beasley or Moore, the Office Action uses the same rationale for combining these references as was set forth in the 35 U.S.C. § 103(a) rejection combining U.S. Patent No. 5,663,167 with Beasley or Moore. As presented above, however, Applicants respectfully submit the lack of reasonable expectation of success and unexpected properties of the claimed invention render the subject matter of claims 1-4, 6 and 7 of U.S. Patent No. 5,663,167 in light of the teachings of Beasley, non-obvious. Further, the claims of the present application are patentably distinct from the claims of U.S. Patent No. 5,663,167. Accordingly, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicant would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

Dated: May 18, 2009

By: /Sean M. Coughlin/

Ivor R. Elrifi, Reg. No. 39,529
Sean M. Coughlin, Reg. No. 48,593
Attorneys for Applicants
c/o MINTZ, LEVIN
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No. 30623